

## ORIGINAL ARTICLE

**Pencil-beam scanning proton therapy for the treatment of glomus jugulare tumours**

Jiří Kubeš, MD, PhD<sup>1,2,3</sup>, Vladimír Vondráček, MSc<sup>1,3</sup>, Michal Andrlik, MSc<sup>1,3</sup> , Matěj Navrátil, PhD<sup>1,3</sup>, Silvia Sláviková, MD<sup>1,2</sup>, Daniel Klika, MD<sup>1</sup>, Alexandra Haas, MD<sup>1,2</sup>, Kateřina Dědečková, MD<sup>1,2</sup>, Kateřina Kopečková, MD, PhD<sup>2</sup>, Barbora Ondrová, MD<sup>1,2</sup>, Eliška Rotnáglová, MD, PhD<sup>1,2</sup>, Štěpán Vinakurau, MD<sup>1,2</sup>, Alexander Grebenyuk, MD, PhD<sup>4</sup>, & Jozef Rosina, MD, PhD<sup>3,5</sup>

<sup>1</sup>Proton Therapy Centre Czech, Prague, Czech Republic

<sup>2</sup>Department of Oncology, 2nd Faculty of Medicine, Charles University Prague and Motol University Hospital, Prague, Czech Republic

<sup>3</sup>Department of Health Care Disciplines and Population Protection, Faculty of Biomedical Engineering, Czech Technical University Prague, Kladno, Czech Republic

<sup>4</sup>Department of Health Protection and Disaster Medicine, Pavlov First Saint Petersburg State Medical University, Saint Petersburg, Russia

<sup>5</sup>Department of Medical Biophysics and Informatics, 3rd Faculty of Medicine, Charles University Prague, Prague, Czech Republic

**Keywords**

glomus jugulare, Head and neck, radiation oncology, proton radiotherapy

**Correspondence**

Michal Andrlik, Proton Therapy Centre Czech, Budínova 1a, Prague 8, 18000, Czech Republic. Tel: +420 607 836 338; E-mail: michal.andrlik@ptc.cz

Received: 6 October 2021; Accepted: 21 July 2022

*J Med Radiat Sci* 0 (2022) 1–7

doi: 10.1002/jmrs.612

**Abstract**

**Introduction:** Glomus jugulare tumours (GJT) are benign tumours that arise locally and destructively in the base of the skull and can be successfully treated with radiotherapy. Patients have a long-life expectancy and the late effects of radiotherapy can be serious. Proton radiotherapy reduces doses to critical organs and can reduce late side effects of radiotherapy. The aim of this study was to report feasibility and early clinical results of 12 patients treated using proton therapy. **Methods:** Between December 2013 and June 2019, 12 patients (pts) with GJT (median volume 20.4 cm<sup>3</sup>; range 8.5–41 cm<sup>3</sup>) were treated with intensity modulated proton therapy (IMPT). Median dose was 54 GyE (Gray Equivalents) (50–60 GyE) with daily fractions of 2 GyE. Twelve patients were analysed with a median follow-up time of 42.2 months (11.3–86.7). Feasibility, dosimetric parameters, acute and late toxicity and local effect on tumour were evaluated in this retrospective study. **Results:** All patients finished treatment without interruption, with excellent dosimetric parameters and mild acute toxicity. Stabilisation of tumour size was detected on MRI in all patients. No changes in symptoms were observed in comparison with pre-treatment conditions. No late effects of radiotherapy were observed. **Conclusion:** Pencil-beam scanning proton radiotherapy is highly feasible in the treatment of large GJT with mild acute toxicity and promising short-term results. Longer follow-up and larger patient cohorts are required to further identify the role of pencil-beam scanning (PBS) for this indication.

**Introduction**

Glomus jugulare tumours (GJT) are benign tumours that grow from the chemoreceptor tissue of the jugular bulb. They are characterised by locally destructive growth into adjacent bones and tissues and frequent recurrence. Their estimated annual incidence has been reported about 0.07 case per 100,000 per year.<sup>1</sup> Surgery with or without preoperative transarterial embolisation may be used in the treatment of GJT, but it has significant morbidity and

mortality.<sup>2</sup> An alternative to surgery is normofractionated external radiotherapy, through which high level of local control can be achieved.<sup>3</sup> However, due to the high probability of long-term patient survival after treatment, patients are very likely to experience serious late toxicity, particularly ototoxicity, neurotoxicity, cognitive dysfunction or dysphagia and possible induction of secondary tumours.<sup>4</sup> Another option is stereotactic radiotherapy (SRT), which can achieve improved dose distribution. However, in general, SRT is only suitable for

small target volumes and delivers low-dose radiation to a large volume of healthy tissue.<sup>5</sup> This limitation could be overcome using proton beam, which offer zero exit dose and lower dose in front of the target volume (Bragg peak). Proton therapy may be technique of choice in reducing the dose to critical organs, especially in larger target volumes and the most in laterally located tumours. The aim of this retrospective study is to evaluate the feasibility, dosimetry, acute and late toxicity and therapeutic response in patients treated with pencil-beam scanning proton radiotherapy. Twelve evaluated patients is the largest study of proton therapy for GTJ.

## Materials and Methods

Between December 2013 and August 2020, 12 patients with GTJ were treated with IMPT and they were evaluated in this retrospective study. Nine patients had unilateral tumours, two had bilateral tumours, and one had a unilateral tumour with liver and lung metastatic involvement at the time of radiation treatment. The median dose was 54 GyE (Gray Equivalents) (50–60 GyE) with daily fractions of 2 GyE. The standards constraints for head and neck region were used, and they were corrected to higher proton radiobiological efficiency by multiplying factor 1.1.<sup>6</sup> These constraints were almost always reached, except the closely spreaded tumours in the case of cochlea and inner ear.

Twelve patients were analysed with a median follow-up time of 42.2 months (11.3–86.7). Median of age was 46.5 years. Ten patients were female, and two patients were male. Eight patients underwent primary proton therapy (due to inoperability), two had previous surgery, two had transarterial embolisation before radiotherapy, and one had photon radiotherapy in the past. Demographic and treatment parameters are shown in Table 1.

## Immobilisation set-up and planning procedures

Patients were irradiated in supine position using standard 5-point thermoplastic masks (Orfit Industries, Wijnegem, Belgium). The planning CT was performed with 1.25 mm slice thickness. Dental fillings and metal teeth bridges were removed prior to planning CT in order to reduce CT artefacts. Gadolinium contrast-enhanced MRI was performed in all cases, and images were fused with the planning CT for target volume delineation purposes.

## Target volume delineation

The contouring of target volumes and at-risk organs was performed using Focal software (Elekta AB, Stockholm, Sweden). The gross tumour volume (GTV) included tumour mass visible on MRI, see Figure 1. The clinical target volume (CTV) was not defined. The planning target volume (PTV) was created by expansion of the GTV by 3–5 mm at the discretion of the attending physician based on uncertainty in CT and MRI image fusion and treatment set-up uncertainty. The following critical organs were contoured and included in treatment plan optimisation: the spinal cord, brain stem, inner ear, brain, pharyngeal constrictors, larynx and parotid glands.

## Dose prescription and treatment planning

The prescribed dose for PTV was 50–60 GyE in 25–30 fractions depending on the extent of the tumour and the decision of the attending physician. Doses were calculated by treatment planning software Xio 4.80 (Elekta AB). Treatment planning system (TPS) is calibrated in physical Gy. Prescription in GyE was recalculated by factor of 1.1 from physical Gy. One or two irradiation fields were used

**Table 1.** Patient demographic and treatment parameters.

	Age	Sex	Fisch–Mattox classification	Previous surgery	Previous radiotherapy	GTV volume (cm <sup>3</sup> )
Pt1	47	F	Di3	No	No	41.9
Pt 2	63	F	De2	Resection	No	10.9
Pt3	72	M	Di2	Decompression craniotomy	Previous RT 50 Gy/25 fractions	22.3
Pt4	39	M	De2	No	No	35.1
Pt5	66	F	Di3	No	No	11.3
Pt6	46	F	Di3	No	No	27.8
Pt7	38	F	De2	Embolisation	No	32.8
Pt8	35	F	C2	2x resection	No	13.8
Pt9	36	F	C4	No	No	34.0
Pt10	44	F	De1	No	No	10.3
Pt11	68	F	B	Embolisation	No	17.7
Pt12	67	F	C2	No	No	8.5



Figure 1. MRI typical tumour location.

depending on the PTV size and location. Single Field Uniform Dose (SFUD) approach was used when possible, otherwise intensity modulated proton therapy (IMPT) optimisation was used to achieve desired dose distribution, see Figure 2. Standard constraints for optimisation were used. Required tolerance doses were met. Only in the case of close proximity of tumour to cochlea or inner ear, the coverage of target volume was

preferred to the detriment of dose load of those critical organs. Two oblique irradiation fields were used or one irradiation field with a 20% dose reduction at the distal edge of the field for the remaining 2 mm to compensate for higher RBE. Each plan underwent pre-treatment patient-related quality assurance (QA) by DigiPhant water phantom using a MatriXX PT (IBA Dosimetry, Schwarzenbruck, Germany) ionisation chamber array detector. Agreement between measured and calculated dose distribution for each field at 3 planes perpendicular to particular beam axis was evaluated by absolute gamma analysis. Planes were selected to represent whole irradiation situation – field entrance, centre of PTV and distal part of PTV. The gamma criteria of dose difference (DD) 3% and distance to agreement (DTA) 3 mm were used. A gamma score less than 1 for at least 95% of evaluation points was taken as threshold for accepting plan for treatment.

Robustness of the treatment plans was not evaluated regularly. Due to experience, the positioning error at this anatomical area is very low so geometrical uncertainty is negligible.

Two orthogonal X-ray images were performed prior to each treatment session. The set-up position was evaluated according to bone structures, and the patient’s position was adjusted using the robotic couch with 6° of freedom.

Control CTs were performed at 1- or 2-week intervals to check the position of structures and body surface. In the case of changes (e.g. change in paranasal cavities filling), quality assurance plans were prepared to evaluate

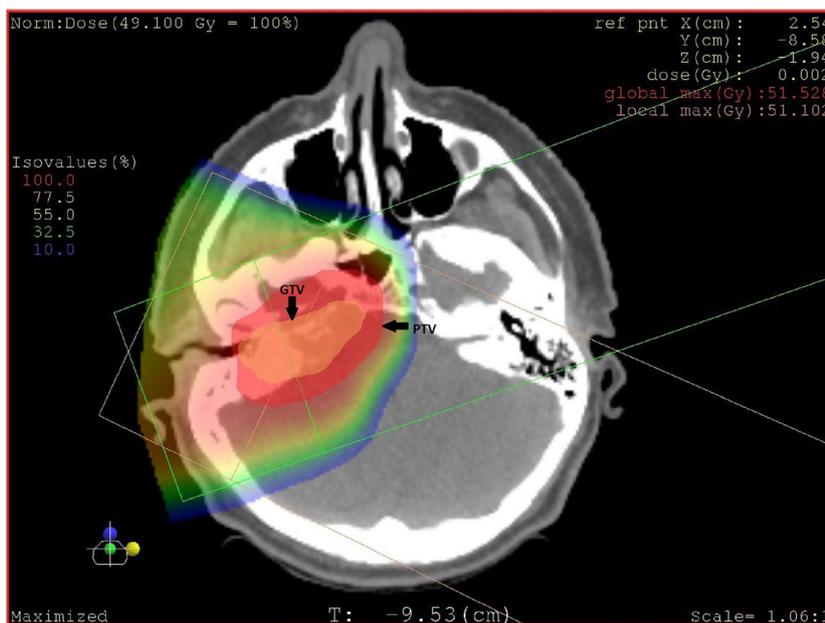


Figure 2. Dose coverage using proton PBS.

the dose distribution changes. Replanning was triggered when the changes within the tumour or surrounding tissues led to a significant change in the planned dose distribution. Replanning was performed when the dose to critical organs was increased by more than 2 GyE or when the decrease in the coverage of PTV ( $PTV_{D98\%}$ ) was bigger than 2 GyE.

At the end of treatment, patients were followed up by their referring physician and annually by a radiation oncologist. Tumour size was assessed once a year by MRI scans. Toxicity was assessed according to the CTCAE scale version 4.<sup>7</sup>

## Results

All patients completed treatment without any interruption. The median follow-up is 42.2 months. Dosimetric parameters for individual plans are presented in Table 2.

Acute toxicity was mild in all patients. Nine of the 12 patients experienced mild skin erythema; no mucositis within the oral cavities was observed. Mild xerostomia was reported by 4 of the 12 patients, and two patients experienced temporary swallowing difficulty that did not require any treatment. Late toxicity (more than 3 months after radiotherapy) has so far been observed in one patient – ipsilateral ototoxicity with a 60% of hearing loss. The mean dose to cochlea was 21 GyE in this case. There is probably no correlation to dose and hearing loss in this case. Any other late toxicities have not been observed. Acute and late toxicity in individual patients is summarised in Table 3.

All patients remain alive at the time of evaluation. No changes in primary tumour size were observed on follow-up MRIs. Necrotic tumour changes were observed in one patient on a control MRI 24 months after radiotherapy.

One patient with primary metastatic disease had progression of metastatic lesions in the lung and liver and received two cycles of peptide receptor radiotherapy (PRRT). This patient is now in partial remission. No worsening of symptoms was observed. Table 4 summarises treatment results.

## Discussion

Glomus jugulare tumours are rare tumours what make their optimal management unclear. Surgical treatment poses risks such as cranial nerve damage, leakage of cerebrospinal fluid and other postoperative complications – especially when dealing with larger tumours.<sup>8–10</sup> Since these tumours are benign with very slow growth and patients usually experience minimal symptoms, these surgical complications have become difficult to tolerate in recent years.

Radiotherapy is a viable alternative to surgery.<sup>11</sup> For instance, in reported treatment results for 88 glomus tumours in 66 patients receiving external radiotherapy with an average dose of 45 Gy/25 fractions (average GTV size was 30 cm<sup>3</sup>), the authors describe 100% tumour control at 5 years and 98.7% control at 10 years. Acute grade 3 toxicity requiring hospitalisation was reported in 13% of patients and late grade 3 toxicity such as carotid and middle cerebral artery stenosis and brain necrosis in 4.5% of patients. We noticed none of these complications.

An alternative to fractionated radiotherapy is stereotactic radiosurgery that can be performed using gamma-knife, cyber-knife or linear accelerators.<sup>5</sup> In reported treatment results using SRT in 46 patients (with a median GTV size of 3.6 cm<sup>3</sup> and median dose of 20 Gy), the authors achieved a 42% improvement in neurological deficit and a reduction in tumour size on

**Table 2.** Dosimetric parameters for PTV and organs at risk for individual patients.

Patient no.	1	2	3	4	5	6 <sup>1</sup>	7 <sup>1</sup>	8	9	10	11	12
<i>Dose [CGE]</i>												
Prescribed dose to PTV	54.00	60.00	60.00	54.00	54.00	50.00	50.00	50.4	54.00	54.00	54.00	50.00
PTV $D_{mean}$	54.90	61.29	60.87	55.08	55.29	44.08	44.51	45.93	54.40	53.812	55.11	51.12
PTV $D_{98\%}$	52.25	57.97	57.42	47.74	50.93	39.82	44.77	8.69	0.00	43.67	52.69	48.07
Spinal cord $D_{2\%}$	15.29	1.76	0.00	3.63	1.57	18.92	31.11	0.11	25.74	10.121	0.88	0.22
Brain stem $D_{2\%}$	52.91	21.23	53.46	52.14	6.05	15.73	22.88	12.32	53.90	22.55	8.36	2.09
Ipsilateral cochlea $D_{mean}$	55.44	53.99	56.76	53.45	46.10	21.23	15.43	36.65	54.55	53.98	55.630	44.96
Contralateral cochlea $D_{mean}$	0.00	0.00	0.00	0.00	0.00	20.36	2.62	0.00	0.00	0.00	0.00	0.00
Ipsilateral parotid gland $D_{mean}$	41.67	44.10	27.57	23.46	27.67	31.81	19.70	0.02	33.07	16.93	14.26	24.32
Contralateral parotid gland $D_{mean}$	0.00	0.00	0.00	0.00	0.00	24.66	13.95	0.00	0.00	0.00	0.00	0.00
Larynx $D_{mean}$	0.22	0.00	0.00	4.08	0.00	14.58	0.00	0.00	0.00	0.00	0.00	0.00
Pharyngeal constrictors	2.01	0.35	0.00	2.43	0.00	24.53	27.09	0.00	0.00	0.00	0.00	0.00

<sup>1</sup>Patients with bilateral tumours.

**Table 3.** Acute and late toxicity (CTCAE v.4 scale).

CTCAE criteria v. 4 scale	Skin (dermatitis)	Mucosa (mucositis)	Parotid gland (xerostomia)	Spinal cord (neuropathia)	Ear (hearing loss)	Eye (conjunctivitis, vision impairment)	Larynx (hoarseness)	Pharynx (dysphagia)
Acute toxicity no of pts								
0	3	12	9	12	10	12	12	10
1	7	0	3	0	2	0	0	2
2	2	0	0	0	0	0	0	0
Late toxicity no of pts								
0	12	12	12	12	10	12	12	12
1	0	0	0	0	1	0	0	0
2	0	0	0	0	1	0	0	0

**Table 4.** Treatment results for individual patients.

	RT dose [CGE]	FU time (M)	FU MRI	Note
Pt1	54.0	55.3	SD	
Pt2	60.0	25.0	SD	
Pt3	60.0	41.7	SD	Necrotic changes on MRI
Pt4	54.0	66.9	SD	
Pt5	54.0	29.6	SD	
Pt6	50.0	51.8	SD	
Pt7	50.0	30.5	SD	
Pt8	50.0	86.7	SD	Dissemination to lung and liver
Pt9	54.0	82.2	SD	
Pt10	54.0	13.7	SD	
Pt11	54.0	11.3	SD	
Pt12	50.0	11.3	SD	

FU, follow-up; SD, stable disease.

follow-up imaging examinations in 42% of patients.<sup>12</sup> In the long-term results for gamma-knife radiosurgery in 75 patients with a median follow-up time of 51.5 months (and average tumour volume of 7 cm<sup>3</sup> with an average dose of 18 Gy), authors described improvement of pre-existing deficits in 15 patients (20%) and stabilisation was noted in 48 patients (64%). Twelve patients (16%) had new symptoms or progression of their pre-existing symptoms, and the main factor associated with a higher risk of developing these complications was tumour size.<sup>13</sup> Additionally in reported treatment results for 30 patients with GJT treated with stereotactic radiotherapy with linear accelerators (with a median follow-up time of 4.6 years, a mean tumour volume of 56 cm<sup>3</sup> with a typical dose of 14 Gy in one fraction), authors described tumour control at 97% with long-term grade 1 toxicity at 13%.

Radiotherapy is therefore an alternative to surgery at more advanced stages (Fisch class C-labyrinth and petrous bone is affected and D-intracranial spreading).<sup>14</sup>

Radiotherapy has lower complication rates and similar or better local control rates in this cases.<sup>15</sup> However, the follow-up period for radiosurgical series is no longer than 5 years – late and very late consequences of radiotherapy may occur through longer observed follow-up times. Fractionated radiotherapy is known to lead to the induction of secondary malignancies such as meningiomas.<sup>16</sup> At present, there exists a lack of information about the possible induction of secondary malignancies after radiosurgery or stereotactic radiotherapy. Another potential complication is vascular damage leading to ischemia or cognitive dysfunction.<sup>17,18</sup> The higher incidence of stroke has not yet been published for SRT for meningiomas.<sup>19</sup> However, follow-up time in this case remains insufficient to exclude this possibility. Furthermore, SRT or radiosurgery is not suitable for large tumours near the brainstem or other critical structures. Volume limits for SRT are not clearly given but range from 10 to 25 cm<sup>6</sup>.<sup>20</sup> All of the above complications are dose-dependent, and their development involves in particular medium and low doses applied to large volumes of healthy tissue. Proton radiotherapy with pencil-beam scanning technology reduces these low-dose bath problems due to a finite range within the tissue. GJTs are usually located laterally, and this localisation maximises the benefit of finite range of protons for radiotherapy. Likewise, this solves the problem of radiotherapy for large tumours since protons have no GTV size limitations.

Due to the very low incidence of GJT and the poor availability of proton therapy, data on the effects of proton therapy are seriously lacking. In fact, the use of proton radiotherapy is described in only one case of glomus tumour.<sup>21</sup> Our retrospective series includes patients with large tumours unsuitable for surgery or stereotactic radiotherapy. Dosimetric parameters demonstrate that even for large tumours treated with proton therapy the dose to critical organs can be significantly reduced. Acute toxicity is minimal and long-term toxicity additionally remains minimal. At time of

writing, no patient has developed tumour progression within the treated area. To the best of our knowledge, this is the largest group of patients treated to date with proton beam therapy for GJT. Due to low number of cases and low incidence of events, survival and incidence analysis was not performed. This is a limitation of this study and can be addressed in future studies.

The disadvantage of the study is its retrospective nature, a small number of patients and its short follow-up time. The use of PBS in the treatment of GJT needs a larger patient group and a longer follow-up period. However, in the case of large tumours unsuitable for SRT using of PBS should be considered.

Proton pencil-beam scanning radiotherapy is feasible in the treatment of large GJT with mild acute toxicity and promising short-term results. The use of PBS appears to be particularly encouraging for younger patients with a long-life expectancy.

## Funding Information

This work was supported by the European Regional Development Fund-Project: 'Engineering Applications of Microworld Physics' (No. CZ.02.1.01/0.0/0.0/16\_019/0000766).

## Conflict of Interest

None declared.

## Ethical Approval

The study was approved by Proton Therapy Centre institutional ethics committee and was conducted according to local ethical standards. All patients signed informed consent with the treatment before inclusion to the clinical registry.

## References

- Ramina R, Maniglia JJ, Fernandes YB, et al. Jugular foramen tumors: diagnosis and treatment. *Neurosurg Focus* 2004; **17**: E5.
- Guss ZD, Batra S, Limb CJ, et al. Radiosurgery of glomus jugulare tumors: a meta-analysis. *Int J Radiat Oncol Biol Phys* 2011; **81**: e497–502.
- Wong BJ, Roos DE, Borg MF. Glomus jugulare tumours: a 15 year radiotherapy experience in South Australia. *J Clin Neurosci* 2014; **21**: 456–61.
- Toda K, Shibuya H, Hayashi K, Ayukawa F. Radiation-induced cancer after radiotherapy for non-Hodgkin's lymphoma of the head and neck: a retrospective study. *Radiat Oncol* 2009; **4**: 21.
- Liscak R, Urgosik D, Chytka T, et al. Leksell gamma knife radiosurgery of the jugulotympanic glomus tumor: long-term results. *J Neurosurg* 2014; **121**: 198–202.
- Bentzen SM, Constine LS, Deasy JO, et al. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. *Int J Radiat Oncol Biol Phys* 2010; **76**(3 Suppl): S3–9.
- [https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03/Archive/CTCAE\\_4.0\\_2009-05-29\\_QuickReference\\_8.5x11.pdf](https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf)
- Huy P, Kania T, Duet R, et al. Evolving concepts in the management of jugular paraganglioma: a comparison of radiotherapy and surgery in 88 cases. *Skull Base* 2009; **19**: 83–91.
- Gottfried ON, Liu JK, Couldwell WT, et al. Comparison of radiosurgery and conventional surgery for the treatment of glomus jugulare tumors. *Neurosurg Focus* 2004; **17**: E4.
- Marangos N, Schumacher M. Facial palsy after glomus jugulare tumour embolization. *J Laryngol Otol* 1999; **113**: 268–70.
- Dupin C, Lang P, Dessard-Diana B, et al. Treatment of head and neck paragangliomas with external beam radiation therapy. *Int J Radiat Oncol Biol Phys* 2014; **89**: 353–9.
- Ibrahim R, Ammori MB, Yianni J, et al. Gamma Knife radiosurgery for glomus jugulare tumors: a single-center series of 75 cases. *J Neurosurg* 2017; **126**: 1488–97.
- Sallabanda K, Barrientos H, RDA I, et al. Long-term outcomes after radiosurgery for glomus jugulare tumors. *Tumori* 2018; **104**: 300–6.
- Mariani-Constantini R (ed). Paraganglioma: a multidisciplinary approach. Codon Publications, Brisbane, 2019.
- Jansen TTG, Timmers HJLM, Marres HAM, et al. Results of a systematic literature review of treatment modalities for jugulotympanic paraganglioma, stratified per Fisch class. *Clin Otolaryngol* 2018; **43**: 652–61.
- Morgenstern PF, Shah K, Dunkel IJ, et al. Meningioma after radiotherapy for malignancy. *J Clin Neurosci* 2016; **30**: 93–7.
- Huang R, Zhou Y, Hu S, et al. Radiotherapy exposure in cancer patients and subsequent risk of stroke: a systematic review and meta-analysis. *Front Neurol* 2019; **10**: 233.
- McDowell LJ, Ringash J, Xu W, et al. A cross sectional study in cognitive and neurobehavioral impairment in long-term nasopharyngeal cancer survivors treated with intensity-modulated radiotherapy. *Radiation Oncol* 2019; **131**: 179–85.
- McClelland S 3rd, Ciporen JN, Mitin T, et al. Long-term stroke risk of single-fraction photon-based stereotactic radiosurgery for meningioma. *Clin Neurol Neurosurg* 2018; **173**: 169–72.
- Hasegawa H, Hanakita S, Shin M, et al. Re-evaluation of the size limitation in single-session stereotactic

radiosurgery for brain arteriovenous malformations: detailed analyses on the outcomes with focusing on radiosurgical doses. *Neurosurgery* 2019; **86**: 685–96.

21. Hankinson TC, Ogden AT, Canoll P, et al. Intraorbital and intracranial soft-tissue glomus tumor in an 8-year-old child. Case report. *J Neurosurg Pediatr* 2008; **1**: 389–91.